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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/840,872 | 04/25/2001 | Antonio J. Grillo-Lopez | P 0280609/2000-30-154A | 4921 |

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PILLSBURY WINTHROP SHAW PITTMAN, LLP
P.O. BOX 10500
MCLEAN, VA 22102

| EXAMINER | |
|---|---|
| UNGAR, SUSAN NMN | |
| **ART UNIT** | **PAPER NUMBER** |
| 1642 | |
| **MAIL DATE** | **DELIVERY MODE** |
| 07/11/2007 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/840,872 | GRILLO-LOPEZ, ANTONIO J. | |
| | Examiner | Art Unit | |
| | Susan Ungar | 1642 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☐ Responsive to communication(s) filed on *30 April 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☐ Claim(s) *56-60 and 62-74* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *56-60 and 62-74* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/30/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

1. The Amendment filed April 30, 2007 in response to the Office Action of November 29, 2006 is acknowledged and has been entered. Previously pending claim 56 has been amended. Claims 56-60, 62-74 are currently being examined.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. The following rejections are being maintained:

***Claim Rejections - 35 USC § 103***

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 56-60, 62-74 remain rejected under 35 USC 103 for the reasons previously set forth in the paper mailed November 29, 2006, Section 5, pages 2-5.

Applicant reiterates the teaches of the prior art of record and summarizes prosecution and points to the Declaration, apparently submitted in response to Examiner's statement that a previous argument had not been found persuasive because no evidence had been presented demonstrating the uncertainty of activity of FcR expressing cells in the CNS, which demonstrates that as of the priority date of the instant application, the use of anti-CD20 antibodies for the treatment of CNS lymphomas was unpredictable due to the compromised activity of immune effector cells in the CNS including FcR-expressing cells.

Applicant argues that contrary to the assertions of the examiner, a skilled artisan would not have believed that there was a reasonable chance of success for the method of the combined references, given that apoptosis induced by anti-CD20 antibodies, unlike apoptosis induced by anti-fas antibodies was understood to be enhanced by Fc receptor expressing cells and at the time of the invention, the augmented level of apoptosis induced by anti CD20 antibodies in the presence of FcR-expressing cells was suggested to contribute to the remission observed in B cell lymphoma patients, inferring that in the absence of functional FcR-expressing cells, the rituximab antibody would not treat CNS lymphoma.

The argument has been considered but has not been found persuasive because although Applicant argues that the known apoptotic function of ritixumab was known to be enhanced by the presence of FcR-expressing cells, given the known direct apoptotic function of ritixumab, one would have a reasonable expectation of successfully treating a CNS lymphoma for the reasons of record. Further, and only in answer to Applicant's arguments, it is noted that contrary to Applicant's arguments and the arguments set forth in the Declarations of record, those of ordinary skill in the art at the time the invention was made recognized that the CNS is not an immuno-priviledged site, that it comprises active immune effector cells including FcR-expressing cells.

In particular, Barnum (Crit Rev Oral Biol Med, 1995, 2:132-146), teaches that the conventional dogma that the CNS is an immuno-priviledged site is not in fact the case. In particular as of 1995, those of ordinary skill in the art knew that the CNS synthesizes and regulates production of complement, wherein definitive evidence is known that astrocytes synthesize components of the complement system. The reference teaches that the astrocyte is comparable to hepatocytes and

cells of the monocyte/macrophage series in terms of the number of components it produces. Further it has been shown that astrocytes act as antigen-presenting cells and that microglia (FcR-expressing cells) have phagocytic capabilities (see p. 132, cols 1 and 2). Thus, it would be expected, given that the CNS comprises the components required for effective function of ritixumab, that the combined references teach and make obvious the claimed invention with a reasonable expectation of success. The issue remains the same, the claimed invention is made obvious by the combined references.

Applicant points to the Shan references and states that the references suggested that *in vivo*, FcR-expressing cells may interact with anti-CD20 antibodies to mediate apoptosis that contributes to the remission observed in lymphoma patients treated with anti-CD20 antibodies. Applicant points out that anti-fas antibodies induce apoptosis in the absence of FcR-expressing cells.

Applicant points to the Relton Declaration, wherein a review of the Declaration reveals that Dr. Relton attests that as of the priority date of the instant application it was known that anti-CD20 antibodies, unlike anti-Fas antibodies, interact with FcR-expressing cells to enhance apoptosis and affirms the findings of the Shan references.

The argument has been considered but has not been found persuasive because the Shan references do not teach or suggest that the anti-CD20 antibodies would not be effective to treat if FcR expressing cells were absent. Further, as set forth above, FcR-expresssing cells are present in the CNS and the combined prior art makes obvious the claimed invention for the reasons set forth previously and above.

Applicant further argues that a skilled artisan would not have reasonable expected that anti-CD20 antibodies would be therapeutically efficacious in the CNS because a skilled artisan could not have been certain that FcR-expressing cells were active in the CNS and points to the Gerber Declaration, previously considered.

The argument and Gerber Declaration were previously considered but not found persuasive for the reasons of record. Further, contrary to the arguments, one of ordinary skill in the art would have been certain that FcR-expressing cells were active in the CNS (see Barnum (Crit Rev Oral Biol Med, 1995, 2:132-146, in particular, p. 132).

Applicant reiterates arguments drawn to the Shan references.

The arguments were previously considered but not found persuasive for the reasons of record.

Applicant argues and the Relton Declaration states that at the time of the present invention, the therapeutic efficacy of anti-CD20 antibodies was known to depend on the induction of cell-mediated immune responses and that it was understood at the time the invention was made that the brain was substantially immunocompromised and one of ordinary skill in the art would not believe that the invention would function as claimed with a reasonable expectation of success.

Applicant reiterates the arguments drawn to the Relton Declaration and the Garber Declaration and the references of record on pages 9-11.

The argument has been considered but has not been found persuasive for the reasons set forth above and for the reasons of record, in particular wherein Barnum teaches that the CNS is not immuno-priviledged, contrary to previous dogma.

As drawn specifically to claims 68-74 which are drawn to labeled anti-CD20 antibodies, Applicant argues that Examiner has not met the burden of establishing a *prima facie* case of obviousness with respect to claims 69-70, reiterates the teachings of Caligiuri and Anderson and further argues that one would not have been motivated to substitute radiolabeled anti-CD20 antibodies of Anderson with the unlabeled anti-Fas antibodies of Caligiuri because the skilled artisan would have been aware of the elevated toxicity risks associated with direct administration of therapeutic agents to the CNS.

The argument has been considered but has not been found persuasive because the claimed invention is obvious for the reasons of record. Further, it appears that Applicant is arguing that the invention of claims 68-74 is not enabled because of the elevated toxicity risks associated with direct administration of therapeutic agents to the CNS. However, Examiner does not agree with Applicant that the claimed invention is not enabled because one of ordinary skill in the art, at the time the invention was made would have been aware, just as Applicant is aware of, and claims, the conventional therapeutics that could be appropriately administered directly to the CNS.

The arguments have been considered but have not been found persuasive and the rejection is maintained.

***Obviousness-Type Double Patenting***

6. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759

F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

7. Claims 56-60 and 62-74 remain rejected under the provisions of Obviousness-Type Double Patenting for the reasons previously set forth in the paper mailed November 29, 2006, Section 6, page 5.

Applicant reiterates arguments set forth above. The argument has been considered but has not been found persuasive for the reasons set forth previously and above.

8. No claims allowed.

9. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE

OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (571) 272-0837. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley, can be reached at 571-272-0898. The fax phone number for this Art Unit is (571) 273-8300.

Susan Ungar
Primary Patent Examiner
June 28, 2007